Remarks

Claims 1-6 and 10-13 were pending in the subject application. By this Amendment, claim 6 has been amended and new claims 15-20 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 10-13, and 15-20 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, the applicant notes that the instant Office Action indicates that claims 1-7 and 10-14 are pending. However, in the applicant's Amendment of December 3, 2003, claims 7 and 14 were cancelled. Thus, once this Amendment is entered, claims 1-6, 10-13, and 15-20 are currently pending. Support for new claims 15, 16, and 20 can be found, for example, at page 2, lines 4-6, and page 4, lines 22-24, of the subject specification as originally filed. Support for new claim 17 can be found, for example, at page 6, lines 7-10, of the subject specification as originally filed. Support for new claim 18 can be found, for example, at page 5, lines 9-12, of the subject specification as originally filed. Support for claim 19 can be found, for example, at page 5, lines 13-18, of the subject specification as originally filed. Claim 6 has been amended to correct an obvious typographical error.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 and Information Disclosure Statement including form PTO/SB/08B. The applicants respectfully request that the reference listed on the form PTO/SB/08B be considered by the Examiner and that such consideration be made of record in the subject application.

Claims 1-6 and 10-13 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicant respectfully submits that the claimed invention is fully enabled by the subject specification.

The applicant respectfully submits that the behavior exhibited by the transplanted hematopoietic stem cells described in the Chopp *et al.* abstract, and their effect on surrounding endogenous cells, reasonably correlates with an improvement in sensory, motor, and/or cognitive function. The experimental results suggest that hematopoietic stem cells have the potential to develop into functional neural cells. As indicated at lines 14-20 of the Chopp *et al.* abstract, the

phenotypic fate of donor cells was determined using immunohistochemistry, which showed that scattered bone marrow (BM) cells, hematopoietic stem cells (HSC), and mesenchymal stem cells (MSC) expressed the neuronal specific markers MAP-2 (microtubule-associated protein-2), NeuN (Neuronal Nuclei protein), NeuroD, TH (tyrosine hydroxylase), and the neurotransmitter GABA (gamma amino butyric acid), and the astrocytic specific marker GFAP (glial fibrillary acidic protein). Expression of these neural markers suggests that the donor cells developed into functional neurons and astrocytes. Immuno-detection of cell-surface markers is an art-recognized technique for the characterization of cells and determination of cell fate. The instant and previous Office Actions cite portions of the NIH publication ("Stem Cells: Scientific Progress and Future Research Developments"). Submitted with the Information Disclosure Statement that accompanies this Amendment is a copy of Appendices E.i. and E.ii. of the NIH publication (pages E1-E11) for the Examiner's consideration. Pages E1-E11 list several markers commonly used to identify stem cells and to characterize differentiated cell types, such as neurons and astrocytes. For example, page E-8 of the NIH publication lists GFAP for identification of astrocytes and MAP-2 for identification of neurons.

The Office Action cites page ES-6 of the NIH publication for its observation that human cells and mouse cells differ in various ways. Although the NIH publication indicates that laboratory conditions favoring growth and specialization of cells may differ among human and mouse cells, the NIH publication does not indicate that the cells exhibit wholly different differentiation patterns *in vivo*. Furthermore, page ES-7 (first column, second paragraph) of the NIH publication acknowledges that some adult stem cells appear to have the capability to differentiate into tissues other than the ones from which they originated. "Reports of human or mouse adult stem cells that demonstrate plasticity and the cells they differentiate or specialize into include: 1) blood and bone marrow (unpurified hematopoietic) stem cells differentiate into the 3 major types of brain cells (neurons, oligodendrocytes, and astrocytes)".

Thus, based on the cited references, there is no rationale for presuming that while mouse hematopoietic stem cells differentiate into neural cells *in vivo*, human hematopoietic stem cells do not exhibit a similar plasticity and would not exhibit a therapeutic effect. Moreover, the applicant submitted the Weimann *et al.* publication with the previous Amendment, which shows that human

bone marrow cells do indeed have the capability of forming effective neural cells in human adult brains.

The Office Action cites the NIH publication as showing that there are difficulties in cell-based transplantation therapies. However, the NIH publication does not indicate that stem cell transplantation will not work. With any type of therapy there are always likely to be issues that need to be resolved; this does not discount the likelihood that a proposed therapy can be achieved. For example, there are many examples of proposed therapies using organic chemicals that are based solely on *in vitro* data, allowing one of ordinary skill in the art to have a reasonable degree of confidence that the therapy will be effective *in vivo*. In the present case, there is no rationale for concluding that the *in vivo* results obtained using animal models (*e.g.*, mice) would not reasonably correlate with human patients particularly in view of the fact that human bone marrow-derived cells form functional neural cells *in vivo*, as demonstrated by the Weimann *et al.* publication. Please note that the Weimann *et al.* publication is submitted herewith simply to confirm the accuracy and sufficiency of the disclosure as set forth in the applicant's specification as filed. The experimental data described in the Weimann *et al.* publication confirms the applicability of the claimed methods to human cells and human patients, with a reasonable expectation of success.

The Office Action cites the Mezey *et al.* publication as evidence of difficulty in using hematopoietic stem cells to treat neurodegenerative disease. However, the Mezey *et al.* publication demonstrates that bone marrow-derived cells play a role in neurogenesis and that at least some of the neurons and glia present in the adult nervous system may be bone marrow-derived (see page 298, first column, of Mezey *et al.*). Page 301 of the Mezey *et al.* publication is cited in the Office Action as highlighting the difficulties with using bone marrow cells for therapy. Although the Mezey *et al.* publication states that growth factor treatment *in vitro* may be necessary to enrich or select for distinct cell types, this is not evidence of difficulty in using bone marrow cells for therapy, but is instead an indication that if specific differentiated cells are required, it is necessary to identify a growth factor that will provide the cells required. The methods of the subject invention involve the use of stem cells, which are undifferentiated and differentiate upon administration into the brain. Therefore, it is unnecessary to obtain distinct cell types prior to administration.

The applicant respectfully submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. Thus, the applicant respectfully submits that the subject specification enables the claimed cell-based transplantation methods.

Accordingly, the applicant respectfully submits that, given the teaching of the specification, one of ordinary skill in the art could make and use the claimed invention without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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GPL/mv
Attachments: Petition and Fee for Extension of Time
Request for Continued Examination
Assertion of Small Entity Status
Information Disclosure Statement, including Form PTO/SB/08 and copy of reference

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